September 30, 2011

The Honorable Hilda Solis
Secretary
United States Department of Labor
200 Constitution Ave, NW
Washington, DC 20210

RE: Comments on RIN 1210-AB44, Group Health Plans and Health Insurance Issuers Relating to Coverage of Preventive Services Under the Patient Protection and Affordable Care Act

Dear Secretary Solis,

We, the undersigned, are pleased the regulations related to the provisions of the Patient Protection and Affordable Care Act regarding preventive health services cover the full range of contraceptive services, including emergency contraception (EC). Contraception has long been proven to safely and effectively prevent unintended pregnancies and related consequences.

According to the U.S. Centers for Disease Control's website, "Unintended pregnancy is associated with an increased risk of morbidity for women, and with health behaviors during pregnancy that are associated with adverse effects."[1] For one, a woman facing an unintended pregnancy may delay prenatal care. Furthermore, 40% of unintended pregnancies end in abortion.[2] Providing women with increased access to contraceptive services in preventive services under this interim final rule is a critical step to decreasing the high incidence of unintended pregnancy in the United States.

Yet no contraceptive method is 100% effective. Emergency contraception provides a safe, effective back-up method that can prevent pregnancy after unprotected sex, unwanted sex, or contraceptive failure. Having multiple options of safe and effective emergency contraception available increases the likelihood that a woman can obtain a product that works for her situation.

Because scientifically unfounded arguments regarding emergency contraception continue to be recycled,[3] we feel compelled to clarify any misunderstandings regarding the currently available methods of emergency contraception and their mechanisms of action.

There are currently three types of emergency contraceptive pills (ECPs) approved by the U.S. Food and Drug Administration[4] for use by American women: progestin-only ECPs, ECPs containing a selective progesterone receptor modulator, and combined ECPs containing both estrogen and progestin.

Progestin-only ECPs have largely replaced the older combined ECPs, which combined estrogen with progestin. Progestin-only ECPs contain the progestin levonorgestrel. The current formulation of Plan One-Step® ECP contains a single 1.5 mg dose of levonorgestrel taken within 72 hours of unprotected sex or contraceptive failure.[5] Next Choice® ECPs are labeled as one .75 mg dose taken within 72 hours after unprotected intercourse and second 0.75 mg dose 12 hours after the first dose.[6,7] Studies have shown continued, but declining, efficacy for both regimens when taken up to 120 hours after unprotected sex.[8] Both regimens have been found to be equally effective.[9]

Levonorgestrel, the active ingredient in progestin-only ECPs, has been widely used in various formulations for over three decades. It has been extensively studied in women of reproductive age. According to the World Health Organization, levonorgestrel ECPs (LNG ECPs) are "safe for use for all

women, including adolescents. Levonorgestrel is well tolerated, is not a known allergen, leaves the body within a few days, is not addictive and has demonstrated no toxic reactions. LNG ECPs pose no risk of overdose and no major drug interactions or contraindications exist for LNG ECPs." [10,11,12,13]

In August 2010, the U.S. Food and Drug Administration (FDA) approved a selective progesterone receptor modulator (SPRM) ulipristal acetate (30 mg in a single dose), marketed as ella® for use as emergency contraception.[14] It is available by prescription only and has been found to be highly effective and well tolerated.[15,16,17] It consists of one pill taken within five days of unprotected sex. It is the first product specifically developed for emergency contraceptive use.

When specifically packaged ECPs are not available, some kinds of regular birth control pills can be used in specific combinations as emergency contraception. Dosage varies by brand. At this time, 19 brands of combined oral contraceptives are approved in the United States for EC use.[18] Additionally, research has also found that that an alternative regimen of ethinyl estradiol and the progestin norethindrone is also safe and efficacious, suggesting that oral contraceptives containing progestins other than levonorgestrel may also be used for emergency contraception by prescription.[19]

Mechanism of Action for Emergency Contraceptive Pills

ECPs do not induce abortion nor do they harm an established pregnancy. ECPs work by delaying or inhibiting ovulation. Respected medical authorities such as the U.S. Health and Human Services Department (HHS), its agencies, and the American College of Obstetricians and Gynecologists (ACOG) all have indicated that pregnancy begins with implantation.[20,21,22]

Progestin-only ECPs have been shown to inhibit the ovulatory process and the luteal function.[23,24,25,26,27] Based on existing animal and human studies, Dr. H. B. Croxatto and colleagues have argued that most—if not all—of the contraceptive effect of progestin-only ECPs can be "explained by inhibited or dysfunctional ovulation."[28] Upon reviewing available research, James Trussell, PhD and Elizabeth G. Raymond, MD, MPH, conclude that, "the best available evidence indicates that levonorgestrel ECPs prevent pregnancy by mechanisms that do not involve interference with post-fertilization events."[29] This conclusion is also echoed by the International Federation of Gynecology and Obstetrics.[30]

For combined emergency contraceptive pills, several clinical studies have demonstrated that estrogen ethinyl estradiol combined with the progestin levonorgestrel also can inhibit or delay ovulation. As is the case with progestin-only ECPs, the combined pills have proven more effective when taken during the first half of the menstrual cycle, before ovulation has occurred.[31] Various studies have explored, with different findings, the additional possible mechanisms of biochemical alterations in the endometrium after treatment, interference with the corpus luteum function, thickening of the cervical mucus resulting in trapping of sperm, and other possible actions in addition to those affecting ovulation.[32] While future research might find an additional mechanism besides inhibited or delayed ovulation at play, it is important to note that the effectiveness and mechanism of action are inter-related. A mechanism would have to include a post-fertilization effect to be 100% effective. Some women will inevitably take ECPs post ovulation and research has demonstrated that ECPs are not as effective when administered post ovulation.[33] The combined ECPs reduce the risk of pregnancy by 75%[34] so therefore cannot include a post-fertilization effect.

Ulipristal acetate (UPA), marketed as ella, is the most effective of currently available ECPs on the US market, with reports of effectiveness ranging from 62% to 85%.[35] This emergency contraceptive lasts

up to 120 hours and, unlike the progestin-only or combined pills, does not decline in effectiveness over that time period, providing women with a wider timeframe to prevent an unintended pregnancy following unprotected, under-protected or unwanted sex.

When taken immediately before ovulation, ella postpones follicular rupture. The likely primary mechanism of action of UPA for emergency contraception is therefore inhibition or delay of ovulation. It is possible that alterations to the endometrium that may affect implantation may also contribute to efficacy.[36]

In sum, as noted on the peer-reviewed www.not2late.com website,[37] "We can't always completely explain how contraceptives work, and it is possible that any of these methods may at times inhibit implantation of a fertilized egg in the endometrium. But the best evidence that we have suggests that levonorgestrel and ulipristal acetate EC does not interfere with post-fertilization events."[38]

Spurious concerns have also been raised alleging that ECPs will harm an existing pregnancy if taken (inadvertently or otherwise) when a woman is already pregnant. There is no scientific evidence supporting this. Indeed, in FDA Advisory Committee deliberations on ulipristal acetate, Dr. David Archer addressed this point. "This is a single dose. There is no signal in the endometrium whatsoever that I can see. Luteal function appears to be adequate in the studies where we've monitored luteal function after administration of this drug or even levonorgestrel. So I just don't think that there is any element here that would allow me to say that this has an abortifacient activity."[39]

Yet opponents of emergency contraception—and we should add, all contraception—continue to try to confuse women by misrepresenting the facts about EC in general and ella in particular. Questions have also been raised in an attempt to link ella to mifepristone. Mifepristone is a different progestin that, when given after a pregnancy has started, will induce an abortion by causing the uterine lining to shed after a fertilized egg is implanted, mifepristone has been approved by the FDA for use in early abortions under the brand name Mifeprex®.[40] ella's primary mechanism of action is preventing pregnancy by delaying ovulation in the first place.

Opponents also try scare tactics regarding the safety of ECPs. After many years of EC use in the United States and in many other countries, with thousands upon thousands of women using the product, no serious adverse reactions have arisen from ECP use, or even repeat ECP use. According to Dr. Trussell and Dr. Raymond, "Certainly, repeated use of ECPs is safer than pregnancy, in particular when the pregnancy is unintended and women do not have access to safe early abortion services."[41]

All told, the inclusion of emergency contraceptive products as preventive services for women under the Patient Protection and Affordable Care Act removes a significant cost barrier and provides more women with options to access scientifically-proven safe and effective methods for preventing unintended pregnancies.

Sincerely,

Reproductive Health Technologies Project
American Society for Emergency Contraception
Association of Reproductive Health Professionals
National Family Planning and Reproductive Health Association
Nurse Practitioners in Women's Health
Physicians for Reproductive Choice and Health

[1] "Unintended Pregnancy." *Centers for Disease Control and Prevention*. Last Updated April 30, 2010. www.cdc.gov/reproductivehealth/unintendedpregnancy/.
[2] "DCR Report: Section C, Resolution of Unplanned Pregnancies." *National Campaign to Prevent Teen and Unplanned Pregnancy*. http://www.thenationalcampaign.org/resources/dcr/Sectionc/DCR_Sectionc.pdf.
[3] "Emergency Contraception, Catholics in Favor, Bishops Opposed." *Catholics for Choice & International Consortium for Emergency Contraception.* October 2010. http://www.catholicsforchoice.org/documents/EmergencyContraceptionCatholicsinFavor.pdf.
[4] Plan B was approved by the U.S Food and Drug Administration (FDA) under NDA 02145 on July 28, 1999 for prescription use. Supplemental approval under NDA 02145-S015 on July 10, 2009 provided dual- labeling requirements whereby women 17 and older can purchase it over-the-counter and teen 16 and younger must have a prescription. (Plan B is now marketed only as a generic under the name Next Choice.) Plan B One-Step was approved by the FDA under NDA 21-998, July 10, 2009, under dual labeling whereby women 17 and older can purchase it over-the-counter and teens 16 and younger must have a prescription. Ulipristal acetate, marketed as ella, was approved by the FDA under NDA 022474 on August 12, 2010 for prescription use only.
[5] "U.S. Food and Drug Administration Approvable Letter for Plan B One-Step." *U.S Food and Drug Administration.* http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/021998s000ltr.pdf.
[6] "Watson Pharmaceuticals Receives FDA Approval for Generic Plan B Over-the-Counter Use." *Pharmaceutical Business Review*. August 28, 2010. http://www.pharmaceutical-business-review.com/news/watson_pharmaceuticals_receives_fda_approval_for_generic_plan_b_for_overthecounter_use_090828
[7] "FDA Approves Generic Prescription-Only Version of Plan B Emergency Contraception for Women Ages 17 and Under." *U.S Food and Drug Administration News Release.* June 24, 2009. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm168870.htm
[8] Practice Bulletin No. 112: Emergency Contraception. *Obstetrics & Gynecology*. 2010: 115:1100-9.
[9] Trussell J and Raymond EG. "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy." June 2011. http://ec.princeton.edu/questions/ec-review.pdf.
[10] "Fact sheet on the safety of levonorgestrel-alone emergency contraceptive pills (LNG ECPs)." *World Health Organization*. 2010. http://whqlibdoc.who.int/hq/2010/WHO_RHR_HRP_10.06_eng.pdf.
[11] Sambol NC, et al. Pharmacokinetics of single dose levonorgestrel in adolescents. *Contraception.* 2006, 74:104-109.
[12] Kook, K, Gabelnick, H, Duncan, G. Pharmacokinetics of levonorgestrel .75 mg tablets. *Contraception*, 2000, 66:73-76.
[13] Grimes DA, Raymond EG, Scott Jones B. Emergency contraception over-the –counter, the medial and legal imperatives. *Obstetrics & Gynecology*. 2001, 98:151-155.
[14] "FDA approves ella™ tablets for prescription emergency contraception." *U.S Food and Drug Administration News Release*. August 13 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm222428.htm.
[15] Creinin MD, Schlaff W, Archer DF, Wan L, Frezieres R, Thomas M, Rosenberg M, Higgins J. Progesterone receptor modulator for emergency contraception: a randomized controlled trial. *Obstetrics & Gynecology*. 2006;108:1089-97.
[16] Fine P, Mathé H, Ginde S, Cullins V, Morfesis J, Gainer E. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. *Obstetrics & Gynecology*. 2010;115:257-63.
[17] Glasier AF, Cameron ST, Fine PM, Logan SJ, Casale W, Van Horn J, Sogor L, Blithe DL, Scherrer B, Mathe H, Jaspart A, Ulmann A, Gainer E. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomized non-inferiority trial and meta-analysis. *Lancet.* 2010;375:555-62.
[18] "Prescription Drug Products; Certain Combined Oral Contraceptives for Use as Postcoital Emergency Contraception." *Federal Register*, 62, 37:8610. February 25, 1997. http://www.hhs.gov/opa/pdfs/opa-97-02-attachment.pdf.
[19] Answers to Frequently Asked Questions: How Emergency Contraception Works. *Not-2-Late*. 2011. http://ec.princeton.edu/questions/index.html.
[20] "Code of Federal Regulations: Part 46 – Protection of Human Subjects." *Department of Health and Human Services.* Revised January 15, 2009. http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#46.102.
[21] "Code of Federal Regulations: Part 46 – Protection of Human Subjects." *National Institutes of Health.* http://history.nih.gov/research/downloads/45CFR46.pdf.
[22] "Statement of Contraceptive Methods ." *American College of Obstetricians and Gynecologists*. July 1998.
[23] Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. *Contraception*. 2001;63:123-9.
[24] Durand M, del Carmen Cravioto M, Raymond EG, Durán-Sánchez O, De la Luz Cruz-Hinojosa L, Castell-Rodríguez A, Schiavon R, Larrea F. On the mechanisms of action of short-term levonorgestrel administration in emergency contraception. *Contraception*. 2001;64:227-34.
[25] Marions L, Hultenby K, Lindell I, Sun X, Ståbi B, Gemzell Danielsson K. Emergency contraception with mifepristone and levonorgestrel: mechanism of action. *Obstetrics & Gynecology*. 2002;100:65-71.

[26] Marions L, Cekan SZ, Bygdeman M, Gemzell-Danielsson K. Effect of emergency contraception with levonorgestrel or mifepristone on ovarian function. *Contraception.* 2004;69:373-7.
[27] Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. *Contraception*. 2004;70:442-50.
[28] Trussell, "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy."
[29] *Ibid*.
[30] "Mechanism of Action: How do levonorgestrel-only emergency contraceptive pills (LNG ECPs) prevent pregnancy?" *International Federation of Gynecology and Obstetrics (FIGO) & International Consortium for Emergency Contraception*. March 2011. http://www.cecinfo.org/publications/PDFs/policy/MOA_ENG_2011.pdf.
[31] Trussell, "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy."
[32] *Ibid.*
[33] *Ibid.*
[34] "Answers to Frequently Asked Questions About: How Effective is Emergency Contraception." *Not-2-Late*. June 2011. http://ec.princeton.edu/questions/eceffect.html.
[35] Trussell, "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy."
[36] "Highlights of Prescribing Information: ella (ulipristal acetate)." *U.S Food and Drug Administration*. August 2010. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022474s000lbl.pdf.
[37] www.not-2-late.com is a peer reviewed, comprehensive emergency contraceptive resource website operated by the Office of Population Research at Princeton University and the Association of Reproductive Health Professionals.
[38] "Answers to Frequently Asked Questions About: How Emergency Contraception Works."
[39] Archer, D, M.D. "FDA Reproductive Health Drugs Advisory Committee Meeting on Ulipristal Acetate (ella)". *U.S Food and Drug Administration*. June 17, 2010. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ReproductiveHealthDrugsAdvisoryCommittee/UCM217418.pdf.
[40] "Answers to Frequently Asked Questions About: How Emergency Contraception Works."
[41] Trussell, "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy."